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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,407	08/01/2003	Douglas W. Losordo	58098 (71417)	6007

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EXAMINER	
O HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/633,407	LOSORDO ET AL.	
	Examiner	Art Unit	
	Eileen B. O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-74* is/are pending in the application.

4a) Of the above claim(s) *4-7,10,14-16,20,22,23,28,29,35,43-65 and 69-74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,8,9,11-13,17-19,21,24-27,30-34,36-42 and 66-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-74 are pending in the instant application. Claims 3, 17, 30 and 31 have been amended as requested by Applicant in the Paper filed February 1, 2007.

Claims 4-7, 10, 14-16, 20, 22, 23, 28, 29, 35, 43-65 and 69-74 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-3, 8, 9, 11-13, 17-19, 21, 24-27, 30-34, 36-42 and 66-68 are currently under examination.

Withdrawn Objections and Rejections

2. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-3, 8, 11-13, 17-19, 21, 24-27, 30-33, 36-42 and 66-68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method for increasing endothelial cell proliferation by administering a compound that will decrease ezrin activity. The claims do not require that the compound possess any particular structure. Thus, the claims are drawn to a genus of compounds that is defined only by activity.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved

until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only Y27632, but not the full breadth of the claims, meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-3, 8, 9, 11-13, 17-19, 21, 24-27, 30-34, 36-42 and 66-68 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record in the previous office action, and below. Applicants traverse the rejection on pages 16-19 of the response and submit that they disclose that disruption of ezrin activity *in vivo* increased endothelial cell proliferation and angiogenesis and blood vessel formation in a mouse hind limb ischemia model as shown in the specification at Example 14 and Figure 13, wherein mice with induced hindlimb ischemia were injected with HUVECs transfected with either wild-type ezrin or with ezrin having a dominant negative mutation that reduced ezrin activity. Mice that received HUVEC having reduced ezrin activity showed a functionally significant increase in blood vessel formation as evidenced by a marked increase in hindlimb perfusion. No such increase in perfusion was observed in mice that received HUVEC transfected with wild-type ezrin. Applicants also submit that following angioplasty, local expression of TNF at sites of arterial injury reduces endothelial cell proliferation and re-endothelialization of the damaged blood vessel (page 39, line 20, to page 40, line 6), and that these negative changes can be blocked by decreasing ezrin activity as evidenced in Examples 12 and 13, where Applicants show that decreasing ezrin activity blocks TNF's suppression of endothelial cell proliferation. In addition, Applicants have shown that blocking RhoA kinase activity using Y27632 reversed ezrin/TNF mediated inhibition of endothelial cell proliferation

(Figure 15C and Example 16, page 47, line 25, to page 48, lines 1-11). Applicants argue that based on these results, one skilled in the art would expect that decreasing ezrin activity should reduce the severity of blood vessel damage when a mammal is exposed to conditions conducive to damaging the blood vessels. Also argued is that the Office's reliance on the Uchida et al. and Shibata et al. references is misplaced because the question of whether or not a reference "teaches away" from Applicant's claimed method is irrelevant to the question of enablement, and the proper test of enablement is whether Applicant's specification teaches one of skill in the art to "make and use" the claimed invention.

Applicants' arguments have been considered but are not found persuasive. Applicant's *in vitro* results indicate that Y27632 could be useful *in vivo* for treating ischemic vascular disease by enhancing endothelial cell growth. However methods of treatment of mammals are more complex. It is not unexpected that the mice receiving HUVECs transfected with a dominant negative mutation had a functionally significant increase in blood vessel formation compared to mice receiving HUVECs transfected with wild-type ezrin. The wild-type ezrin HUVECs would be expected to behave like the endogenous endothelial cells; that is, TNF would induce ROCK-2, and ROCK-2 would phosphorylate enzrin both in the endogenous cells and the transplanted HUVECs, causing inhibition of cell proliferation in those cells. However, in mice receiving HUVEC cells containing a dominant negative mutation of ezrin, the endogenously produced TNF would not be able to affect the dominant negative mutant ezrin in the HUVECs, as shown in Example 12, resulting in cell proliferation from those HUVECs. However, for claims requiring administering a compound that decreases ezrin activity, the proper control in the *in vivo* experiment of Example 14 would be dividing the hindlimb ischemia mice into two groups,

one that would receive a composition comprising Y27632, and one that would receive a control composition that does not contain Y27632 after establishing hindlimb ischemia. This is what Shibata et al. did in their study on vascular injury in rats. Shibata et al. decreased the activity of ezrin by administering the kinase inhibitor Y27632, but found it had no effect on reendotheliazation.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. The criteria set forth in Ex parte Forman (230 USPQ 546 (Bd. Pat. App. & Int. 1986) and reiterated in In re Wands (858 F.2d 731,737,8 USPQ2d 1400, 1404 (Fed. Cir 1988), include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

All the Wands factors are considered and it is the balance of factors that determines whether a disclosure enables the use of the invention. In the previous Office Action, all of these factors were considered.

The MPEP states in section 2164.02:

"Lack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art."

In the instant case, an *in vitro* experiments are not predictive of treating a mammal with a compound that decreases ezrin activity, for the reasons discussed in the previous Office Action.

Applicants are enabled for the method in Example 14, treatment with HUVEC cells containing a dominant negative mutation of ezrin. For these reasons, the rejection is maintained.

It is believed that all pertinent arguments have been answered.

Conclusion

5. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nichol can be reached at (571) 272-0835.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to

the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner

Eileen B. O'Hara

EILEEN B. O'HARA
PRIMARY EXAMINER